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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,608	07/05/2007	Richard Lennox Boyd	NOR-021US/286336.160	6002

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EXAMINER
LI, QIAN JANICE

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/553,608	BOYD ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-70* is/are pending in the application.

4a) Of the above claim(s) *39,44, 46, 50-53,55,56,59-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-38, 40-43, 45, 47-49, 54, 57, 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I drawn to a method for improving tolerance in a graft recipient is acknowledged. Applicant also elected a species for examination defined by a combination of the following elements: administering leuprolide and CD34+ hematopoietic stem cells into a patient whose thymus is at least in part atrophied and further administering a cytokine KGF.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 33-70 are pending, claims 33-38, 40-43, 45, 47-49, 54, 57, 58 read on the elected invention and species. Claims 39, 44, 46, 50-53, 55, 56, 59-70 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 33-38, 40-43, 45, 47-49, 54, 57, 58 are under current examination.

Specification

The abstract of the disclosure is objected to because it does not commence on a sheet separate from other materials of the disclosure. Correction is required. See MPEP § 608.01(b). The cover page of a PCT publication is no longer acceptable by the Patent publication branch at the USPTO.

The first section of the specification refers to multiple applications in the continuation chain. The status of each application should be updated.

Claim Objections

Claim 33 is objected to because of the claim recitation, "the donor graft without thymus reactivation". Assuming the phrase "without thymus reactivation" defines the graft, and a graft would not have a thymus.

Claim 48 is objected to because of the following informalities: LHRH should be spelled-out the first time it appears in the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-38, 40-43, 45, 47-49, 54, 57-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim recitation, "a *mismatched* donor". The specification fails to define the term "mismatch", it is uncertain, in what aspect the donor and recipient mismatches, and thus the metes and bounds of the claims are unclear. In view of the teaching of the specification, it is suggest using terms such as "allogeneic" and "xenogeneic" in place of "mismatch".

Claims 39 and 40 recite "the cytokine". There is insufficient antecedent basis for this limitation in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33-38, 40-42, 47-49, 54, 57 are rejected under 35 U.S.C. 102(b) as being anticipated by *Ghalie et al* (Am J Hematol 1993;42:350-3).

Ghalie et al teach a method comprising ablating the patient's T cells by total body irradiation and cyclophosphamide (Patient Characteristics, page 361), reactivating the patient's thymus by administering LHRH agonist leuprolide intravenously or orally in a pharmaceutical composition before, at the time, or after receiving donor cells (Leuprolide Administration, page 361), which would reactivate thymus through disruption of sex steroid-mediated signaling to the thymus; wherein the patient's thymus has been at least partially deactivated due to the age of the patients and by the high-dose chemotherapy and total body irradiation, wherein the patients are post-pubertal (median age 26), wherein the thymus would have been at least partially atrophied, and received allogeneic transplantation. Accordingly, *Ghalie et al* anticipate instant claims.

Please note that the claim recitation "for improving tolerance in a patient to a graft from a mismatched donor" has not been given patentable weight in this rejection and rejections that follow. This is because it merely recites an intended use of the method, wherein there is no structural or manipulative difference between the claimed invention

and the prior art in order to patentably distinguishing the claimed invention from the prior art. **If the prior art structure is capable of performing the intended use, then it meets the claim.** In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Claims 33-38, 40, 41, 42, 47-49, 54, 57 are rejected under 35 U.S.C. 102(b) as being anticipated by *Nara et al* (Acta Haematol 1994;92:42-5).

Nara et al teach a method for treating refractory pure red cell aplasia in a post-pubertal patient, comprising ablating the patient's T cells by immune suppressive agents such as cyclophosphamide (e.g. abstract), supplementing the repeated blood transfusion by administering LHRH agonist buserelin acetate in a pharmaceutical carrier (page 43, column 2), which would reactivate thymus through disruption of sex steroid-mediated signaling to the thymus; wherein the patient's thymus has been at least partially deactivated due to the age of the patient and chemotherapy for the autoimmune anemia, and wherein the patients received allogeneic transplantation (blood transfusion from a mismatched donor). Accordingly, *Nara et al* anticipate instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 33-38, 40-43, 45, 47-49, 54, 57, 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Mardiney, III et al* (USP 6,863,885), in view of the BBC News (December 1998), and *Windmill et al* (Tissue Cell. 1998;30:104-11); and evidenced by *Pinski et al* (J Androl 1993;14:164-9, abstract).

Mardiney, III et al teach a method for allogenic (mismatched donor) graft (inducing tolerance to a graft) comprising administering hematopoietic growth factors and cytokines, ablating the patient's T cells by non-myeloablative dose of radiation or chemotherapy, followed by hematopoietic stem cell transplantation. *Mardiney, III et al* teach the radiation eradicates diseased blood cells, while the growth factor promotes the regeneration of new blood cells (e.g. column 3). *Mardiney, III et al* established the state of the art with respect to inducing tolerance to allogenic grafts, which is a pre-conditioning regimen that includes either high dose radiation/chemotherapy or a lower dose non-myeloablative regimen accompanied by hematopieitic growth factors and cytokines (e.g. claims). *Mardiney, III et al* go on to teach the goal of a pre-conditioning regimen is to eliminate diseased cells such as leukemia/lymphoma, to create an environment in the recipient in which the donor's HPCs can successfully engraft by homing into the recipient's bone marrow to further undergo hematopoiesis, and serve as an immunosuppressive agent to mitigate graft rejection in the treatment of non-cancerous diseases (e.g. column 1). *Mardiney III, et al* do not teach using thymus reactivation in the transplantation procedure.

The cited BBC News supplemented the deficiency by establishing it was known in the art that chemical castration via sex hormones can restore/regenerate thymus

function and thus be used at the time of transplantation to promote the recovery of immunosuppressed recipient. Although the News did not give details about castration and thymus regeneration, the teaching of *Windmill et al* evidenced that it was known in the art before the instant priority date, castration could increase the weight of thymus, as well as the numbers and responsiveness of T cells in peripheral blood (e.g. abstract), and it was also known in the art sex hormones are closely interrelated with thymus function and immune system (Introduction and Discussion).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Mardiney, III et al*, by combining the chemical or surgical castration in the transplantation protocol with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so for added benefit of restoring the recipient hemotopoietic system or in complex clinical cases, where additional measurement to ensure the success of stem cell transplantation is required. Although the combined teachings do not specify the LHRH antagonists known in the art, it would have been obvious to the skilled in the art the LHRH antagonists as recited in claim 49 was known in the art to be capable of decreasing serum testosterone to castration levels as evidenced by *Pinski et al*. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 33-38, 40-43, 45, 47-49, 54, 57, 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Laporte et al.* (Bone Marrow Transplant 1998;S1:S76-7), in

view of *Beschorner et al.* (Transplant 1991;52:879-84) and *Marchetti et al.* (Endocrinol 1989;125:1037-45).

Laporte teaches a method for improving tolerance (preventing graft-v-host disease, GVHD) in a patient to a graft from a mismatched donor comprising pre-conditioning post-puberty patients with total body-irradiation, cyclosporine (both depleting immune cells of patients) and G-CSF, followed by cord blood hematopoietic stem cell transplantation. *Laporte* teaches all patients achieved full chimerism (e.g. the abstract). *Laporte* established the state of the art with respect to inducing/improving tolerance to allogenic grafts, which includes a pre-conditioning regimen comprising either or both radiation/chemotherapy accompanied by hematopieitic growth factors and cytokines. *Laporte* teaches CsA was used for pretreatment (e.g. the abstract), but still 3 out of 6 patients developed GVHD, but incidents and severity were lower compared. *Laporte* does not teach using thymus reactivation in the transplantation procedure for improving tolerance.

Beschorner supplemented the deficiency by establishing it was known in the art that there is a correlation between the use of CsA and development of GVHD, and such was associated with changes thymus (e.g the abstract and figure 1a-b). Hence it is desirable to promote thymic recovery after administration of CsA for improving tolerance (see e.g. the abstract). *Beschorner* did not use LHRH agonist for promoting thymic recovery.

Marchetti supplemented *Laporte* in view of *Beschorner* by establishing it was known in the art that LHRH agonist such as Deslorelin could restore age-associated

thymus atrophy (column 1, page 1038). *Marchetti* teaches chronic treatment with LHRH-A deslorelin reversed the age-related decreases in both thymus weight and thymic LHRH-binding sites (e.g. table 1 and figure 1).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method taught by *Laporte* with that of *Marchetti* as suggested by *Beschorner* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so for preventing GVHD in a patient of graft recipient. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Laporte et al.* (Bone Marrow Transplant 1998;S1:S76-7), in view of *Beschorner et al.* (Transplant 1991;52:879-84) and *Marchetti et al*. (Endocrinol 1989;125:1037-45) as applied to claims 33-38, 40-43, 45, 47-49, 54, 57, 58 above, further in view of *Panoskaltsis-Mortari et al*. (Blood 1998;92:3960-7).

The combined teaching was detailed *supra*, which did not teach using KGF for improving graft tolerance.

Panoskaltsis-Mortari supplemented the deficiency by establishing it was well known in the art KGF administered before conditioning ameliorates GVHD after allogeneic bone marrow transplantation (e.g. figures 2-3).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include KGF in the method taught by *Laporte* in view of

Marchetti and *Beschorner* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so for maximizing the effect of preventing GVHD in a patient of graft recipient. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Laporte et al.* (Bone Marrow Transplant 1998;S1:S76-7), in view of *Beschorner et al.* (Transplant 1991;52:879-84) and *Marchetti et al*. (Endocrinol 1989;125:1037-45) as applied to claims 33-38, 40-43, 45, 47-49, 54, 57, 58 above, further in view of *Blacker et al*. (Acta Endocrinol 1991;125:581-9).

The combined teaching was detailed *supra*, which did not teach using leuprolide for thymus recovery.

Blacker supplemented the deficiency by establishing it was well known in the art continued administration of leuprolide was capable of increasing thymus weight and decreasing estradiol (e.g. table 1).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use leuprolide in the method taught by *Laporte* in view of *Marchetti* and *Beschorner* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so for maximizing the effect of preventing GVHD in a patient of graft recipient. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI** whose telephone number is 571-272-0730. The examiner can normally be reached on 9 AM -7:00pm, Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on 571-272-0739. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Q. JANICE LI/
Primary Examiner, Art Unit 1633